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Research Article

Biliary Vs Non-Biliary Risk Factors of Development of Acute Necrotizing Pancreatitis as a Sequel of Acute Pancreatitis Episode in a Tertiary Care Center

Mahdi Albander[1]*, Naseem Abusharifa[2], Razan Alomar[3], Reema Alsogair[3], Rahaf Alghannam[3], Deem Alkalid[3] and Aljohrah Alanazi[4]

[1]*Consultant Minimally Invasive Surgery, Robotic in Gastrointestinal, Colorectal and Bariatric Surgery, Assistant Professor of General Surgery, Deputy Head of General Surgery, King Saud Medical City, Riyadh, Saudi Arabia*

[2]*Almaarefa University, College of Medicine, Riyadh, Saudi Arabia*

[3]*College of Medicine, King Saud bin Abdulaziz University for Health Sciences (KSAU-HS), Ministry of National Guard Health Affairs (MNGHA), Riyadh, Saudi Arabia*

[4]*Dar Al Uloom University, College of Medicine, Riyadh, Saudi Arabia*

***Corresponding Author:** Mahdi Albander, Consultant Minimally Invasive Surgery, Robotic in Gastrointestinal, Colorectal and Bariatric Surgery, Assistant Professor of General Surgery, Deputy Head of General Surgery, King Saud Medical City, Riyadh, Saudi Arabia.

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Abstract

Background: Necrotizing pancreatitis is associated with high rate of morbidity and mortality that could be a leading cause of serious complications such as cholangitis, ileus, bowel ischemia, formation of pseudoaneurysm, hemorrhage and venous thrombosis. Therefore, identification of different possible risk factors is essential as it help in early diagnosis and management. This study aimed to identify possible risk factors to develop necrotizing pancreatitis including both biliary or non biliary risk factors after presenting as case of acute pancreatitis.

Methods: This study is a retrospective cohort study which will include all patients admitted to King Saud Medical City, Riyadh Saudi Arabia, with diagnosis of acute and necrotizing pancreatitis, male and female, aged more than or equal to 18 years old A customized data collection sheet will be used to collect relevant data. A p value of less than or equal to 0.025 will considered significant.

Results: The prevalence of gallbladder disease and stones in this study was found to be 19.3% and 39.4% respectively. Around 13.1% of the subjects had a history of pancreatitis and 2.7% had developed an infection. In the overall sample, 12.01% of the patients (n = 34) had developed Necrotizing Pancreatitis (NP), (82.4%) were males (P-value: 0.005), alcoholics (32.5%) (p-value: 0.02), and (41.2%) were diabetics (23.3%; p-value: 0.025). Surprisingly, a lower proportion of the patients with NP had gallbladder disease (14.8%) or gallbladder stones (20.6%) (P-value: 0.04). In addition, the distribution of continuous variables such as WBC (P-value: 0.027), serum glucose (P-value: 0.02), blood urea nitrogen (P-value: 0.001), serum calcium (P-value: 0.001), serum lactase (P-value: 0.001), LDH (P-value: 0.0001), and serum lipase (P-value: 0.032) was significantly different for patients with and without NP. Findings of binary regression analysis showed that males (OR = 4.89; [95% CI: 2.18 - 10.96]), alcoholics (RR = 2.49; [95% CI: 1.13 - 5.53]), and diabetic patients (RR = 2.30 [95% CI: 1.09 - 4.84) were more likely to develop NP. Patients with gallbladder stones and gallbladder disease were 49% and 85% less likely to develop NP, respectively (RR = 0.41; 95% CI: 0.17 - 0.98). The significant risk factors of NP after making adjustments were found to be gender (male) (aRR = 2.89; 95% CI: 1.11 - 7.50), diabetes history (aRR = 2.17; 95% CI: 0.99 - 4.76), and history of pancreatitis (aRR = 2.59; 95% CI: 1.01 - 6.60).

Conclusion: Risk factors that were correlated positively with development of Necrotizing pancreatitis (NP) after an acute pancreatitis (AP) episode were being male (RR = 3.46), alcoholic (RR = 2.49), and have diabetes mellitus (RR = 2.3), initial presentation with septic picture (RR = 3.83). on the other hand, patients with gallbladder disease or stone were less likely to develop NP as a sequel of AP.

Keywords: *Necrotizing Pancreatitis; Risk Factors; Biliary; Non Biliary*

Introduction

Acute pancreatitis (AP) is one of the leading causes of ER visits characterized by inflammation of the pancreas or the peripancreatic tissue; if not treated, AP could lead to devastating complications including necrotizing pancreatitis in which part of the pancreas or the area around it becomes necrotic [1,2]. Prognosis of necrotizing pancreatitis is poor and mortality range is about 15% up to 30 - 39% in most serious cause of necrotizing pancreatitis. Development of necrotizing pancreatitis increases the risk of secondary infections, multiple organ failure and fetal outcomes [3-5]. The high mortality rate in necrotizing pancreatitis is associated with several risk factors, for instance, being elderly, overweight, activated systemic inflammatory response, high level of creatinine, blood urea nitrogen, glucose, or low levels of serum calcium, and albumin [6,7]. The overall mortality of pancreatitis approximately is 1% [8,9], on the other hand the mortality rate increases to range between 30 - 40% in hospitalized patients with pancreatitis along with organ failure or pancreatic necrosis [10]. A recent systematic review concluded that the overall incidence of acute pancreatitis raised up by 3.07% per year in the last 56 years [11].

Previous literatures have reported that acute pancreatitis causes are also linked to the occurrence of necrotizing pancreatitis; these include gallstone disease primarily and alcohol abuse [12,13]. Moreover; the existing literature suggests that hypertriglyceridemia-induced acute pancreatitis may result in more severe necrotizing pancreatitis than any other etiology [14]. Although it has been investigated, the role of genetic predisposition, previous use of nutritional support, need for early and aggressive fluid replacement, and presence of comorbidities, it is still controversial [12,15].

The relevance of the above-mentioned factors for necrotizing pancreatitis has not been properly investigated in the middle eastern (or Saudi Arabian) population. Thus, proper identification of necrotizing pancreatitis is crucial for early diagnosis, treatment, and ultimately improving patient outcomes. This study aims to identify biliary vs. non-biliary risk factors for the development of complications in necrotizing pancreatitis in patients admitted to a tertiary care center. No previous studies done to identify risk factors for development of necrotizing pancreatitis in Riyadh Saudi Arabia.

Aims and Objectives

To identify possible biliary and non-biliary risk factors for the development of complications in mild, moderate, severe necrotizing pancreatitis patients.

Methodology

A retrospective cohort study will be conducted in King Saud Medical City, Riyadh, Saudi Arabia including all patients with diagnosis of necrotizing pancreatitis either infected or sterile, aged more than or equal to 18 years old and admitted to the hospital between January 2016 and September 2022. A total of 283 patients were included. Data were collected using a customized data sheet by Excel 2016 and data were collected after reviewing computerized medical files and paper-based files of the patients without using any identifiers. Baseline demographics such as age, gender, nationality, weight, height was collected. In addition to past medical, surgical, social history, and laboratory investigations were also included. Moreover, CT scoring index and Balthazar score was also used to predict the severity and grade of necrotizing pancreatitis. Patients with incomplete files or patients younger than 18 years old were excluded from this study.

Ethical consideration

No informed consent was needed since it is a chart review study, no patient direct contact was made by research PI or co-authors. Patient's privacy and confidentiality was maintained throughout the study; no identifiers were used. Patients' information including their Medical Record Numbers and names were substituted with serial number and all information kept and secured in password protected computers, and was accessible only by the research team.

Statistical methods

To describe the characteristics of the study population, we reported frequencies and proportions. More specifically, we reported frequencies and proportions to describe the characteristics of the study population for the categorical variables such as gender, presence of diabetes or hypertension, and bar charts were created for the primary outcome of necrotizing pancreatitis, etc. We checked the normality assumption for continuous variables by histograms superimposed with the normal curve. We reported median and interquartile range (IQR) since data were skewed for the continuous variables of interest. We used a Pearson Chi-squared test or Fisher's exact to assess

the frequency distribution and the relationship between covariates and necrotizing pancreatitis. Since the continuous variables were not normally distributed we performed the Mann-Whitney U test for having the P-values for the differences between patients with and without necrotizing pancreatitis. We performed a univariable regression analysis to determine the biliary and non-biliary risk factors of necrotizing pancreatitis and the independent effect of each significant predictor on necrotizing pancreatitis. We considered a p-value of less than 0.25 for significant results for the binary logistic regression analysis. Finally, we conducted a multivariable logistic regression analysis to determine the biliary and non-biliary risk factors of necrotizing pancreatitis after adjusting for sociodemographic and clinical characteristics. We presented the results of regression analysis by crude/unadjusted risk ratios (RR) and adjusted risk ratio aRR) with 95% Confidence Intervals (CIs). We used SPSS 25.0 to analyze the data.

Results

Sociodemographic and clinical characteristics of the study participants

Table 1 reveals the sociodemographic and clinical characteristics of study subjects in this retrospective cohort study. The median age of the patients was 42 years with an IQR of 23 Years. We found that around more than half of the patients (59.4%) were males and of Saudi nationality (55.9%) as sown in table 1. A similar proportion of the study subjects were smokers (19.8%) and alcoholics (17.8%). Moreover, 24.3% of the patients were diabetic and 21.8% were hypertensive. The prevalence of gallbladder disease and stones was found to be 19.3% and 39.4% respectively. Around 13.1% of the subjects had a history of pancreatitis and 2.7% had developed an infection. On the other hand, only 2% had sepsis and a history of trauma each, and 7.7% had a history of malignancy. In addition, one-third (35.4%) had ERCP and 40.8% had any surgical intervention, whereas 3.7% had a history of chemotherapy. In the overall sample, 12.01% of the patients (n = 34) had developed necrotizing pancreatitis as shown in table 1. Moreover, the median value of serum albumin, serum calcium, blood urea nitrogen, and serum glucose were 33.4 (IQR: 3), 1.18 (IQR: 1), 4.5 (IQR: 4), and 8.4 (IQR: 6) respectively as shown in table 1.

Categorical Variables	n	%
Gender		
Male	240	59.4
Female	164	40.6
Nationality		
Non-Saudi	178	44.1
Saudi	226	55.9
Smoking Status		
Non-Smoker	324	80.2
Smoker	80	19.8
Alcohol Consumption		
Non-Alcoholic	332	82.2
Alcoholic	72	17.8
Hypertension		
No Hypertension	316	78.2
Hypertension	88	21.8
Diabetes		
No	306	75.7
Yes	98	24.3
Cardiac Disease		
No	375	92.8
Yes	29	7.2
Gallbladder Disease		
No	326	80.7
Yes	78	19.3
Gallbladder Stones		
No	245	60.6

Yes	159	39.4
History of Pancreatitis		
No	351	86.9
Yes	53	13.1
Infection		
No	393	97.3
Yes	11	2.7
Sepsis		
No	396	98
Yes	8	2
Pregnancy		
No	395	97.8
Yes	9	2.2
History of Trauma		
No	396	98
Yes	8	2
Malignancy		
No	373	92.3
Yes	31	7.7
Surgical Intervention		
No	239	59.2
Yes	165	40.8
ERCP		
No	261	64.6
Yes	143	35.4
Chemotherapy history		
No	389	96.3
Yes	15	3.7
Continuous Variables	**Median**	**Interquartile Range**
Age (Years)	42	23
WBC	13	8
HCT	41.2	9
Serum Albumin	33.4	8
Serum Glucose	8.4	6
Blood Urea Nitrogen	4.5	4
Serum Creatinine	69	30
Serum Calcium	1.18	1
Serum Amylase	540.64	1088
Serum Lactase	2	2.6
AST	77	162
ALT	66.3	241
LDH	321.67	339
Serum Lipase	474	1126

Table 1: *Sociodemographic and clinical Characteristics of the study participants.*

Biliary and non-biliary risk factors of study subjects by necrotizing pancreatitis

Table 2 illustrates the biliary and non-biliary risk factors of patients in relation to necrotizing pancreatitis. We found that a higher proportion of the patients with necrotizing pancreatitis (82.4%) were males when compared with 17.6% of the females with necrotizing pancreatitis (P-value: 0.005). Similarly, 32.5% of the patients with necrotizing pancreatitis were alcoholic compared to 16.1% of the patients without necrotizing pancreatitis (p-value: 0.02). A significantly higher proportion of patients who with necrotizing pancreatitis (41.2%) were diabetic compared with patients without necrotizing pancreatitis (23.3%; p-value: 0.025). Surprisingly, a lower proportion of the patients with necrotizing pancreatitis had gallbladder disease (14.8%) or gallbladder stones (20.6%) when compared with 16.5% and 38.6% of patients without necrotizing pancreatitis respectively (P-value: 0.04) as shown in table 2. However, there were no significant differences between patients with and without necrotizing pancreatitis by factors such as malignancy, surgical intervention, ERCP, and infection or sepsis as shown in table 2. In addition, the distribution of continuous variables such as WBC (P-value: 0.027), serum glucose (P-value: 0.02), blood urea nitrogen (P-value: 0.001), serum calcium (P-value: 0.001), serum lactase (P-value: 0.001), LDH (P-value: 0.0001), and serum lipase (P-value: 0.032) was significantly different for patients with and without necrotizing pancreatitis. However, the other markers such as serum albumin, creatinine, HCT, AST, and ALT did not significantly differ by necrotizing pancreatitis.

	Necrotizing Pancreatitis				
	Yes		No		P-value
Variables	n	%	No	%	
Gender					
Male	28	82.4	143	57.4	0.005
Female	6	17.6	106	42.6	
Nationality					
Non-Saudi	19	55.9	101	40.6	0.09
Saudi	15	44.1	148	59.4	
Smoking Status					
Non-Smoker	26	76.5	196	78.7	0.76
Smoker	8	23.5	53	21.3	
Alcohol Consumption					
Non-Alcoholic	23	67.6	209	83.9	0.02
Alcoholic	11	32.4	40	16.1	
Hypertension					
No Hypertension	25	73.5	198	79.5	0.42
Hypertension	9	26.5	51	20.5	
Diabetes					
No	20	58.8	191	76.6	0.025
Yes	14	41.2	58	23.3	
Cardiac Disease					
No	31	91.2	230	92.4	0.81
Yes	3	8.8	19	7.6	
Gallblader Disease					
No	33	97.1	208	83.5	0.04
Yes	42	14.8	41	16.5	
Gallbladder Stones					
No	27	79.4	153	61.4	0.04
Yes	7	20.6	96	38.6	

Infection					
No	33	97.1	242	97.2	0.97
Yes	1	2.9	7	2.8	
Sepsis					
No	32	94.1	245	98.4	
Yes	2	5.9	4	1.6	0.1
History of Pancreatitis					
No	26	76.5	215	86.3	0.13
Yes	8	23.5	34	13.7	
Malignancy					
No	33	97.1	223	89.6	0.16
Yes	1	2.9	26	10.4	
Surgical Intervention					
No	25	73.5	144	57.8	0.08
Yes	9	26.5	105	42.2	
ERCP					
No	23	67.6	161	64.7	0.73
Yes	11	32.4	88	35.3	

Table 2: *Sociodemographic and clinical characteristics of study subjects by necrotizing pancreatitis.*

Biliary and non-biliary risk factors with the necrotizing pancreatitis: Findings of binary regression analysis

Table 3 shows the findings of binary regression analysis with respect to the biliary and non-biliary risk factors with necrotizing pancreatitis. We found that males were 3.46 (OR = 4.89; [95% CI: 2.18 - 10.96]) times more likely to develop necrotizing pancreatitis than female patients. The risk of developing necrotizing pancreatitis was 1.86 times among non-Saudi patients than in Saudi patients (RR = 1.86; [95% CI: 0.90 - 3.52]). Likewise, alcoholic patients were 2.49 times more likely to develop necrotizing pancreatitis than non-alcoholic patients (RR = 2.49; [95% CI: 1.13 - 5.53]). Similarly, diabetic patients were 2.3 times more likely to develop necrotizing pancreatitis when compared to nondiabetic patients (RR = 2.30 [95% CI: 1.09 - 4.84]). Patients with gallbladder stones and gallbladder disease were 49% and 85% less likely to develop necrotizing pancreatitis respectively than patients without gallbladder stones (RR = 0.41; [95% CI: 0.17 - 0.98]) and with no gallbladder disease (RR = 0.51; [95% CI: 0.20 - 1.16]). The risk of developing necrotizing pancreatitis was 3.83 times (RR = 3.83; [95% CI: 0.67 - 21.74]) among patients with sepsis than patients without sepsis. (Table 3). On the other hand, factors such as malignancy, infection, surgical intervention, chemotherapy, ERCP, and lab tests such as HCT, serum albumin, and serum creatinine were not found to be significantly associated with necrotizing pancreatitis.

Variable	Risk Ratio	95% CI		P-value
Age	0.99	0.97	1.02	0.75
Gender				
Female	1			
Male	3.46	1.38	8.65	0.008
Nationality				
Saudi	1			
Non-Saudi	1.86	0.9	3.52	0.09
Smoking Status				
Non-Smoker	1			
Smoker	1.14	0.48	2.65	0.76

Alcohol Consumption				
Non-Alcoholic	1			
Alcoholic	2.49	1.13	5.53	0.02
Hypertension				
No Hypertension	1			
Hypertension	1.39	0.61	3.18	0.42
Diabetes				
No	1			
Yes	2.3	1.09	4.84	0.028
Cardiac Disease				
No	1			
Yes	1.17	0.33	4.19	0.81
Gallbladder disease				
No	1			
Yes	0.15	0.2	1.156	0.07
Gallbladder Stones				
No	1			
Yes	0.41	0.17	0.98	0.04
History of Pancreatitis				
No	1			
Yes	0.95	0.81	4.65	0.13
Infection				
No	1			
Yes	1.04	0.12	8.78	0.97
Sepsis				
No	1			
Yes	3.83	0.67	21.74	0.13
Malignancy				
No	1			
Yes	0.26	0.03	1.98	0.19
Surgical Intervention				
No	1			
Yes	0.49	0.22	1.1	0.08
ERCP				
No	1			
Yes	0.87	0.41	1.88	0.73
Chemotherapy history				
No	1			
Yes	0.72	0.09	5.84	0.76
HCT	1.04	0.98	1.09	0.14
Serum Albumin	0.95	0.89	1.01	0.11
Serum Creatinine	0.99	0.99	1	0.58

Table 3: *Biliary and non-biliary risk factors of necrotizing pancreatitis: Univariate analysis.*

Association of biliary and non-biliary risk factors with the necrotizing pancreatitis: Findings of multivariable regression analysis

Table 3 demonstrates the association between biliary and non-biliary risk factors with necrotizing pancreatitis after making adjustment. The potential and significant risk factors of necrotizing pancreatitis were found to be gender (male), diabetes history, and history of pancreatitis. More specifically, a statistically significant association was found between male gender (aRR = 2.89; [95% CI: 1.11 - 7.50]) and necrotizing pancreatitis in the adjusted model as shown in table 3. After making adjustment for other risk factors, we found that patients with diabetes were 2.17 times likely to develop necrotizing pancreatitis than patients without diabetes (aRR = 2.17; [95% CI: 0.99 - 4.76]. Similarly, patients with a history of pancreatitis were 2.59 times likely to develop necrotizing pancreatitis than patients without history of pancreatitis (aRR = 2.59; [95% CI: 1.01 - 6.60].

Discussion

In the past several years the prevalence and the risk factors for pancreatic diseases have been increased which by nature can lead to necrotizing pancreatitis, hence this study aimed to describe the biliary and non-biliary risk factors that can lead to necrotizing pancreatitis in King Saud hospital in Riyadh.

The median age was 42 years old with most of the patients being male with Saudi nationality (59.4%). Of all study population, 19.8% were smokers and 17.8% were alcoholics. In one of the studies done in the Hospital of Nanchang University, 142 eligible patients were enrolled, with the average age of 55.87 ± 15.47 years and the majority were males (52.11%), moreover; 5.63% were patients with alcoholic pancreatitis (5.63%) [16]. Another study in Nantes University hospital in France, that included 148 patients, the average age of the patients was 54.1 years old (17.5%) with male predominance 107 (72.3%) [17].

Out of the total patients who developed necrotizing pancreatitis, males were associated with 3.46 higher risk of development of NP with p-value of 0.005. Furthermore, 32.5% of these patients were alcoholics compared to 16.1% of the patients without necrotizing pancreatitis (p-value: 0.02) and diabetics 41.2% (p-value: 0.025). Therefore, being alcoholic will increase the likelihood by 2.49 to develop NP when compared to non-alcoholic patients, and 2.3 higher risk to get NP in diabetic patients compared to non-diabetic patients. A study done by Garret., *et al*. the most common reported factors that led to necrotizing pancreatitis in their population were alcohol abuse 64 (43,2%) and biliary factors 48 (32,4%) which was found to be associated with many co-morbidities such as hypertension 58 (39,2%), diabetes mellitus 20 (13,5%), dyslipidemia 38 (25,7%), and smoking 54 (36,5%) [17].

Consistent with a study by Stojanovic., *et al*. that showed comorbidities like diabetes were a potential risk factor for the development of necrotizing acute pancreatitis [15].

A surprising finding in our study population that patient who had gallbladder disease (14.8%) or biliary stones (20.6%) were less likely to develop NP when compared with 16.5% and 38.6% of patients without Necrotizing Pancreatitis respectively (P-value: 0.04). There are no studies done to in this area, however biliary stones are a well-established risk factor for the development of acute pancreatitis, and it is accounted to be seen in almost half of 4.8 - 24.2 cases of AP per 100,000 cases occurring in western countries [18-21].

On the other hand, ERCP, which is a well-known risk factor for acute pancreatitis, was mentioned in Głuszek., *et al*. study which stated that 7.7% develop acute pancreatitis post-ERCP, in addition to severe course seen in 31% of the patients, whereas in our study it was noticed that ERCP was not associated with development of necrotizing pancreatitis after severe acute pancreatitis [22]. Furthermore, serum albumin, creatinine, and HCT were not considered as risk factors of necrotizing pancreatitis in our patients, but Stojanović., *et al*. concluded that HCT levels higher than 50% of upper normal was proven to be a predictor of infection in early disease course and was an independent risk factor for infected pancreatic necrosis secondary to necrotizing pancreatitis [15,22-24]. Similarly, hypoalbuminaemia in early stages lead to development of necrotizing pancreatitis and was associated with poor prognosis [15].

It is noteworthy to mention that patients who presented initially septic or developed sepsis during hospital stay had 3.83 more likelihood to develop necrotizing pancreatitis when compared with non-septic patients. This can be explained by secondary infection and sepsis development due to bacterial contamination of pancreatic necrosis which increased the overall mortality up to 80%, not to mention that the incidence of secondary infection and sepsis correlate with extent of pancreatic necrosis [23].

A considerably large numbers of studies have reported that local complications including necrosis in the first episode of acute pancreatitis increase the risk of recurrence [25,26]. Cho., *et al*. found that local complications were the strongest risk factors for recurrent pancreatitis [27]. In this study, similarly, it was found that a previous history of pancreatitis was associated with necrotizing pancreatitis. A possible explanation of this finding is that the first episodes of pancreatitis increase the rate of recurrence to 17%, which in turn can potentially be complicated by necrotizing pancreatitis [25].

Conclusion

Necrotizing pancreatitis is associated with high morbidity and mortality; thus, identification of possible risk factors aid in early detection and possible successful management and reduction in complication rate. In this study, being male, alcoholic, and diabetic were significantly associated with developments of NP as a sequel of AP, and the risk ratio were 3.46, 2.49, 2.3 retrospectively. Moreover, initial presentation to emergency department with features of sepsis increases the likelihood of development of NP by 3.83 in comparison with patients without sepsis. Intriguingly, majority of our patients were with gallbladder disease 49% and 81% with biliary stones had lower risk to develop NP.

Conflicts of Interest

No conflicts of interest to be declared.

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